Advanced MRI Techniques to Assess Sleep Deprivation Vulnerability among Soldiers and Potentially Enhance Performance with Real-Time Biofeedback

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ABSTRACT

NATO needs better methods of measuring and predicting human performance, as well as novel methods of training soldiers that might enhance performance. New breakthroughs with magnetic resonance imaging (MRI) show promise in both areas.

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Rationale: Our group initially [1-3] and now at least three others [4-6], have demonstrated that a baseline fMRI scan while subjects are performing a task can predict who will respond poorly or well after sleep deprivation (SD). That is, the degree a person activates specific brain regions while performing a task when fully rested is related to and can predict their performance under a stressful condition like sleep deprivation (SD). We discuss whether more research in this area might develop this into a useful vocational screening tool.

Related to this concept, researchers have recently developed the ability to perform real-time fMRI, where they analyze and display brain activity immediately as a subject performs a task within the scanner. Going further, researchers can now feed this regional performance data back to a subject as a visible thermometer on the side of the screen while they are in the scanner performing the task, and allow them to use the real-time regional brain activation feedback to modify and improve their task performance. Once could theoretically combine the knowledge of which regions sleep deprivation resilient soldiers use during a task, and 'teach' sleep deprivation vulnerable soldiers with fMRI biofeedback how better to mitigate sleep deprivation vulnerability.

Description of methods employed and results obtained: Over the past year, we have developed methods to detect brain activity during MRI scanning and to feed those activity levels back to participants during the scan. This "real-time feedback" allows participants to adjust their performance based on their own brain activity, with the aim to increase brain activity. We have completed a preliminary study with 12 healthy young adults in a 3 Tesla Siemens MRI scanner and have ongoing research to further optimize brain feedback protocols. In the preliminary study, we first completed a baseline scan where participants were asked to imagine moving their right hand. In the second and third scans, participants were given real or false feedback (counterbalanced order) regarding their brain activity in left premotor brain cortex. Often brain activity decreases with repeated scanning, perhaps due to fatigue effects. We found that brain activity with real feedback remained at baseline levels in left premotor cortex, while brain activity with false feedback decreased. We hypothesize that brain feedback training can be used to enhance performance or maintain performance at baseline levels despite fatigue.

Conclusions: These studies open the possibility of using baseline MRI to screen candidates such as pilots for specific tasks with special skill requirements that may be sleep deprivation sensitive. Further, the newer results with realtime fMRI biofeedback open up the possibility of potentially training soldiers to use brain circuits in a way that is less vulnerable to sleep deprivation. Realtime fMRI, merged with simulators, other training tools or even focal non-invasive brain stimulation, might be used to enhance training and performance and improve resilience to sleep deprivation.

1.0 INTRODUCTION

Depriving someone of sleep for over 24 hours causes performance changes during a variety of tasks [7, 8]. For example, a meta-analysis from 143 studies with a total sample size of 1932 subjects suggests that overall, sleep deprivation (SD) strongly impairs human function. Moreover, performance following SD varies on different types of tasks, including cognitive, motor, and mood aspects. Finally, many factors, such as the length of SD, the complexity of tasks, and the age and gender of subjects influence the effects of SD [7]. Although age and lifestyle factors including sleep debt [9] may influence SD vulnerability, new evidence suggests that SD vulnerability differs widely across individuals [10, 11], and is a consistent trait within individuals over time . A test at rested baseline to determine SD vulnerability would be helpful in effective vocational education, particularly in appropriately choosing soldiers, such as pilots, who may be required to perform complex and quick tasks under sleep deprived conditions. An effective screening tool would also help

promote SD research into the neurobiological mechanisms behind SD vulnerability, and help focus research into why there are between individual differences, and potentially develop more effective sleep deprivation countermeasures.

2.0 WHICH TASKS TO MEASURE

Different cognitive tasks are variably susceptible to sleep loss.[12] In general, simple monotonous tasks associated with cognitive speed, psychomotor skills, and visual and auditory attention are most sensitive to SD. These effects have been explored in terms of reaction time (RT) [13, 14], vigilance [15], sustained attention [16], mental arithmetic [13], working memory [17], tracking ability [18], speech [19] and mood [13]. In contrast, complex and high-level decision-making tasks, which are essentially rule-based, such as critical reasoning [20] and logical convergent tasks, have been suggested to be resilient to SD [21].

Importantly, even during the same cognitive tasks and control conditions, large variations in individual responsiveness to sleep loss have been observed [10, 11, 22]. For example, in an acute SD study, Morgan noted that, following 44 hours of continuous wakefulness, the multiple-task performance of some subjects was degraded by as much as 40 percent while the performance of others was essentially unaffected [22]. In a chronic SD study, Balkin et al. reported that systematic sleep restriction also produced differential amounts of degradation in different subjects [10]. Recently, Caldwell et al. showed that, after 26 - 37 hours of SD, even in well-trained, fully-experienced, military fighter pilots, the flight-simulator performance was not uniformly affected and individual impairments ranged from 135 percent in one case to only 0.6 percent in another [11]. The mechanism or mechanisms responsible for the individual variability of neurobehavioral functioning following SD is still poorly understood. Many factors, especially the interaction of the homeostatic and circadian systems, as well as genetic differences, may contribute to the variations in individual performance.

An important factor in many if not most neurobehavioral tasks is working memory, along with sustained attention. Neurocognitive functioning is severely impaired or fails without these two components. Working memory has been thought to be controlled by a central executive system [23-25]. Executive attention has been suggested by some to derive from a primarily supervisory aspect of working memory [25, 26]. Performance on working memory tasks has been reported to account for many aspects of language comprehension [27, 28] and to predict performance on a range of other cognitive tasks [26]. Consequently, it has been argued that performance on working memory tasks may reflect a fundamental aspect of cognition. It thus may help to explain, at least in part, why monotonous tasks that rely heavily on high levels of sustained attention and working memory are more sensitive to sleep loss than are more complex tasks that require a higher level of cognition in addition to these basic functions.

3.0 RECENT WORK WITH NEUROIMAGING TO FIND CHANGES IN BRAIN ACTIVATION PATTERNS AFTER SLEEP DEPRIVATION

Recently, much recent work to better understand the effects of SD has focused on working memory, given that working memory is involved in most simple and complex cognitive tasks. Functional neuroimaging approaches have enabled investigators to directly investigate changes in brain activation following SD [29-33]. To date, only a few published functional imaging studies have investigated the human brain response to working memory with sleep-deprived subjects. Habeck et al explored 48 hours of SD effects using event-related fMRI during a delayed-match-to-sample task. Because of their particular design and interest, the results entailed activation from all components involved in task performance (such as memory scanning, binary decision, response selection and motor output process) and were not constrained uniquely to working memory [34]. Using positron emission tomography (PET) during a series of addition / subtraction tasks before and after 24 hours

of SD, Thomas et al found a significant decrease in global cerebral metabolic rate for glucose (CMRglu) and a significant decrease in both absolute and relative regional CMRglu in the prefrontal cortex (PFC), posterior parietal cortex (PPC), and thalamus [35]. Utilizing functional magnetic resonance imaging (fMRI) during arithmetic tasks, Drummond and colleagues found a marked decrease in blood oxygenation level dependent **(**BOLD) signal after 35 hours of SD in regions involved in arithmetic working memory, such as the bilateral PFC, parietal cortices, and premotor areas (PMA). Moreover, a significantly decreased performance on arithmetic tasks was also found following SD relative to following a normal night of sleep [32].

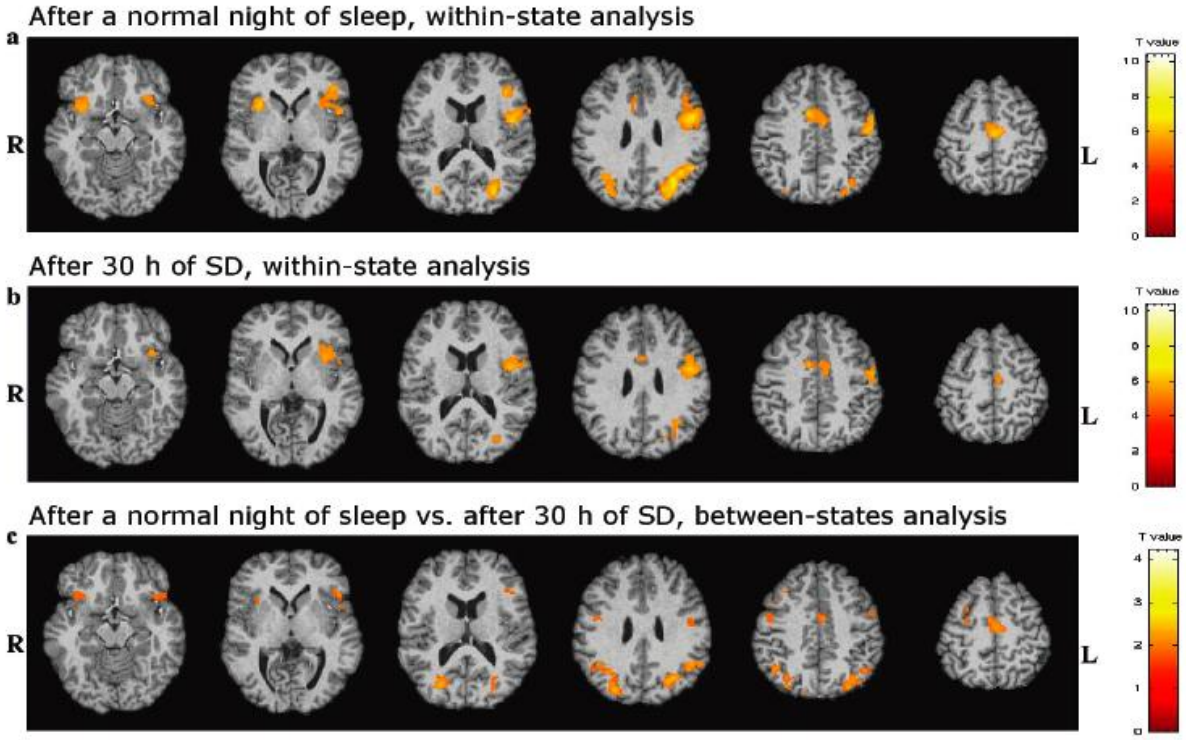

Figure 1: From Mu, Nahas et al, 2005, showing decreased activation overall following SD. Significant brain activation identified by within-state analysis and between-states analysis. Maps are displayed at 6 different brain levels (from 16 mm below to 64 mm above the bicommissural plane). a. After a normal night of sleep, within-state analysis. Map was thresholded at P < .005 (corrected for multiple comparisons). Significant activation (Sternberg task > control) was found in bilateral posterior parietal cortex (PPC), left dorsolateral prefrontal cortex (PFC), left Broca's area, and left supplementary motor area (SMA) (partly involved in right SMA, left premotor area (PMA), and bilateral anterior cingulate gyri), and right ventrolateral PFC. No deactivation (control > Sternberg task) was found. Note that the right dorsolateral PFC was not activated at this threshold; however, it was significantly activated when the threshold was lowered to uncorrected P < .001 with a spatial extent of P < .05 (corrected for multiple comparisons). b. After 30 hours of sleep deprivation (SD), within-state analysis. Map was thresholded at P < .005 (corrected for multiple comparisons). Significant activation was only found in left dorsolateral PFC, Broca's area, SMA, and inferior parietal cortex. No deactivation (control > Sternberg task) was found. c. Between the rested and SD states analysis. Map was thresholded at P < .01 with a spatial extent of P < .05 (corrected for multiple comparisons). Significant difference in activation (normal sleep > SD) was found in bilateral dorsolateral PFC, PPC, SMA, and PMA, left Broca's area, and right ventrolateral PFC. No deactivation (SD > normal sleep) was found. Note that there are more activations (number of activated voxels) differences in the bilateral parietal cortices than other regions. Also note that the right dorsolateral PFC and PMA show significant differences in regional activation, which were not significant at the map after a normal night of sleep at the threshold of corrected P < .005.

Mu et al used 3T fMRI to scan 33 men (mean age, 28.6 ± 6.6 years) on three occasions – at screening baseline, and then immediately before and after 30 hours of SD.[3] Subjects performed the same Sternberg working memory task at the 3 states within the magnetic resonance imaging scanner. Neuroimaging data revealed that, at the screening and rested states, the brain regions activated by the Sternberg working memory task were remarkably similar in magnitude and were the left dorsolateral prefrontal cortex, Broca's area, supplementary motor area, right ventrolateral prefrontal cortex, and the bilateral posterior parietal cortexes. After 30 hours of sleep deprivation, the activations in these brain regions significantly decreased, especially in the bilateral posterior parietal cortices. Task performance also decreased. A repeated-measures analysis of variance revealed that subjects at the screening and rested states had similar activation patterns, with each having significantly more activation than during the sleep-deprivation state. These results suggest that human sleep-deprivation deficits are not caused solely or even predominantly by prefrontal cortex dysfunction and that the parietal cortex, in particular, and other brain regions involved in verbal working memory exhibit significant sleep-deprivation vulnerability. These initial results have now been replicated by others [4-6].

4.0 STUDIES USING BASELINE IMAGING TO PREDICT SLEEP DEPRIVATION VULNERABILITY

In an important DARPA funded study, our group[2] used the then new technology of 3 Tesla fMRI to test whether SD vulnerable individuals have greater SD induced brain changes, and different baseline patterns, than SD resilient individuals, we investigated the differences in brain activation patterns at the rested baseline and SD conditions during a Sternberg working memory task (SWMT) [36, 37] in a SD-vulnerable group and in a SD-resilient group. The SWMT shows changes following SD [17, 38] and has been widely used as a verbal working memory task in functional neuroimaging studies [39-41]. Building on functional imaging studies that have demonstrated that SD decreased both brain activation and performance in working memory tasks [32, 35, 42], we thus hypothesized that the SD vulnerable group would show greater brain activity differences following SD compared to baseline than the SD resilient group. Additionally, based on reports linking performance improvements with increases in working memory capacity [26, 27, 43-47], we further hypothesized that at the rested baseline as well as the SD state, the SD-resilient group would exhibit significantly more global activation than the SD-vulnerable group.

Although there have been numerous studies [48-51], there are not established baseline predictors of who is most vulnerable to the effects of SD. In this study, we examined whether differences in patterns of brain activation under normal sleep conditions relate to the differences in vulnerability to SD. We scanned 33 healthy young men while they performed the Sternberg working memory task (SWMT) following a normal night of sleep and then again following 30 hours of SD. From this initial group, based on the performance of SWMT, we selected 10 subjects resilient to SD (SD-resilient group), and then selected 10 age and education–matched subjects who were vulnerable to SD (SD-vulnerable group). We blindly compared the two groups in terms of brain activation at the rested baseline and during the sleep-deprived states. As hypothesized, following SD, both groups showed significant decreases in global brain activation (in terms of both number of voxels meeting a significance threshold and the number of regions activated, compared to their rested group baseline. At the rested baseline, the SD-resilient group had significantly more brain activation overall than did the SD-vulnerable group. Interestingly, the SD-resilient group after SD had global activation equivalent to the baseline of the SD-vulnerable group. SD induced a significant performance decrement within the SD-vulnerable group and a non-significant change within the SD-resilient group. These preliminary data suggested that patterns of brain activation during the SWMT at the rested baseline state, as well as during the sleep-deprived state, differ across individuals as a function of their SD vulnerability. Functional imaging might therefore be able to predict SD vulnerability.

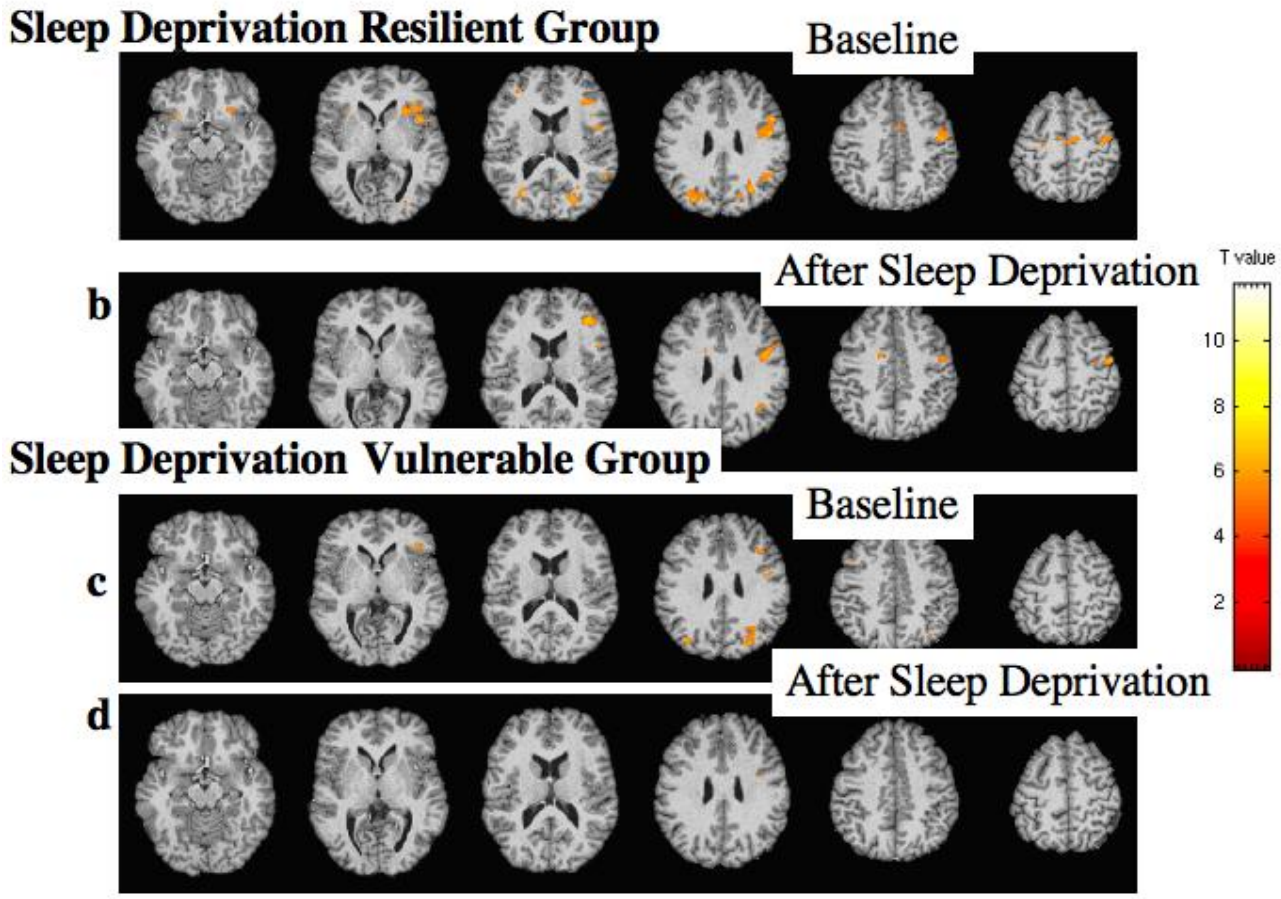

Figure 2 From Mu, Mishory et al, 2005 showing significant within group working memory brain activation maps in the SD-vulnerable group and SD-resilient group, before and after sleep deprivation. Maps were thresholded at the identical $p < 0.001$ with a spatial extent of $p < 0.05$ (corrected for multiple comparisons) and displayed at 6 different brain levels (from 16 mm below to 64 mm above the bicommissural plane). (**a**) SD-resilient group after a normal night of sleep; (**b**) SD-resilient group after 30 h of sleep deprivation SD-resilient group; (**c)** SD-vulnerable group after a normal night of sleep; (**d**) SD-vulnerable group after 30 h of sleep deprivation. SD: sleep deprivation.

In the SD-resilient group, after a normal night of sleep, the SWMT task induced significant activation in brain regions involved in verbal working memory in the left DLPFC (Brodmann areas (BA) 9, 45, 46), left PPC (BA 7, 40), left VLPFC including Broca's area (BA 44), left SMA (the activation in left SMA, extended partly to right SMA (BA 6)), left PMA (BA 6), bilateral anterior cingulate gyri (BA 32)), left cerebellum, right inferior PPC (BA 40), and right ventrolateral PFC (primarily in the inferior frontal gyrus, BA 44. After 30 hours of SD, significant activation was still found within this SD resilient group in the left DLPFC, VLPFC, SMA, and left PPC. No new activated regions were found compared to the group rested baseline.

In contrast, in the SD-vulnerable group, after a normal night of sleep, the SWMT task induced significant activation in brain regions involved in verbal working memory in the left DLPFC (BA 9, 45, 46), left PPC (BA 40), left VLPFC (Broca's area) (BA 44), right inferior PPC (BA 40), and right ventrolateral PFC (BA

44). Notably missing were the activations in the left/right SMA and left PMA seen in the SD-resilient group. After 30 hours of SD, the SD vulnerable group the left DLPFC was the only area to be significantly activated. No new activated brain regions were found.

Perhaps the most important aspect of this study was that at rested baseline, an independent-samples t test revealed that the SD-resilient group had significantly more global activation than did the SD-vulnerable group (899 significant voxels ± 122 in the SD-resilient group; 228 ± 67 in the SD-vulnerable group; $p < 0.001$). Following 30 hours of SD, an independent-samples t test between the two groups showed that the SD-resilient group still had significantly more activation than the SD-vulnerable group (223 significant voxels ± 34 in the SD-resilient group; 5 ± 4 in the SD-vulnerable group; $p < 0.001$).

This was likely the first functional neuroimaging study to quantitatively describe changes in brain activation in a SD-resilient and SD-vulnerable group.[2] Confirming our pre-study hypothesis, we found changes within groups after 30 hours of sleep deprivation relative to their normal sleep baseline. There were also between group differences both following SD and at rested baseline. Consistent with previous verbal working memory imaging studies [39-41], after a normal night of sleep, performing the SWMT resulted in significant activation in the bilateral prefrontal and posterior parietal circuits in both the SD-resilient group and the SD-vulnerable group. At the rested baseline, the SD-resilient group showed significantly more global activation in the number of activated voxels as compared to the SD-vulnerable group, however, there was no significant difference in performance (RTs) between the two groups. In agreement with previous imaging studies on working memory [32, 35], following 30 hours of SD, both the two groups showed significant decreases in global activation, expressed as the number of activated voxels. Moreover, at the SD state, the SD-resilient group had significantly more activation than did the SD-vulnerable group, the RTs in the SD-vulnerable group became significantly longer than in the SD-resilient group. This decrement in performance in the SD-vulnerable group coincides with previous imaging studies in sleep-deprived subjects [32, 34, 35] in which significant decrements in performance were observed. Interestingly and notably, the SD-resilient group after 30 hours of no sleep still had global activation comparable to the SD-vulnerable group at their rested baseline condition. Consequentially, the SD-resilient group in the sleep-deprived state had brain activation equivalent to the SD-vulnerable group at the rested baseline. These results are consistent with the idea that a certain threshold of activation is needed to perform some cognitive tasks and that activation beyond this threshold may maintain the normal performance, but these increases beyond threshold may not produce any better performance, at least during this verbal working memory task.

Others have now tested these results for replication, and have extended them into individual prediction studies [4-6].

In an exciting extension of the Mu et al working memory fMRI study, Caldwell and colleagues again used 3T fMRI to examine the activation of military pilots whose sleep deprivation vulnerability previously had been quantified.[52] A Sternberg Working Memory Task (SWMT) was completed alternately with a control task during a 13-minute blood oxygenation level dependent (BOLD) fMRI scan. The pilots were considered to be not-SD as they had not experienced any recently quantifiable sleep deprivation. Consequently, upon examination of the activated voxels in response to SWMT indicated that, as a group, the pilots appeared similar to the non-pilot subjects in the baseline and rest conditions although they were more similar to fatigue-resistant non-pilots than to fatigue vulnerable non-pilots. Within the pilots, cortical activation was significantly related to sleep deprivation vulnerability as assessed with prior simulator flight performance. These preliminary data suggest baseline fMRI-scan activation during a working memory task may correlate with sleep deprivation vulnerability.

5.0 NEUROBIOLOGICAL MECHANISMS OF SD VULNERABILITY

It is beyond the scope of this manuscript to fully discuss the possible neurobiological mechanisms of this between individual vulnerability, which appears to be a lifelong trait. Exciting new work involving genetics (particularly CLOX genes) should be integrated with any future studies [53].

6.0 RECENT ADVANCES WITH REAL-TIME fMRI

Real-time fMRI feedback allows participants to modify brain activation throughout the course of an fMRI session [54, 55]. One challenge in such feedback studies is clarifying that changes in activation are the result of the feedback, rather than from other confounds such as fatigue or practice effects with repeated scanning. We examined the effect of feedback by providing both true and false feedback in a blinded, counterbalanced method. In a proof of concept study, we selected an imagine-movement task. We hypothesized that true feedback would enhance modification of brain activity, while false feedback would not.

Data was acquired on a 3T Siemens Trio MRI using standard fMRI parameters. The participant was asked to imagine right hand movement during the tasks periods, without actually moving the hand. A brace was used to insure limb immobility. Each scanning session consists of three block-design scans (10 volumes of rest alternated with 10 volumes of imagine movement task, TR = 2.2 s). The first scan was used to functionally localize a region of interest within left Brodmann area 6 (L BA 6, premotor or supplementary motor cortex). In a randomized order, the second and third scans provided either true or false feedback regarding the percent signal change in the selected region of interest. The feedback is presented visually during the imagined movement condition (Figure 3). Participants are instructed to utilize the feedback to increase signal change, while blinded to whether the feedback is true or false. Post-hoc data analysis was performed using FSL FEAT 5.98.

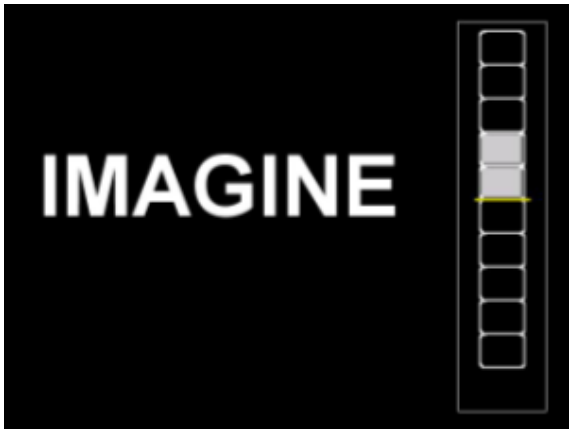

Figure 3: Example of Feedback with Imagine Movement Task – Participants are prompted to perform task by text ("IMAGINE"), while feedback regarding brain activity is provided by scaled-gauge on right of the display screen. Participants are instructed to attempt to increase activation above baseline (yellow-line on scaled-gauge) as much as possible.

Data was acquired on 12 participants, but two were excluded due to motion > 3mm. Using a template mask created around each individual's baseline activity in the NO_FEEDBACK condition, the whole brain, or global, activated voxel count decreased significantly with the two subsequent feedback scans. Our primary region of interest (ROI) was one comprised of all the voxels within L BA 6. In this ROI, activation was

consistent (no significant differences) for the NO_FEEDBACK and REAL_FEEDBACK conditions but significantly different for the FALSE_FEEDBACK condition.

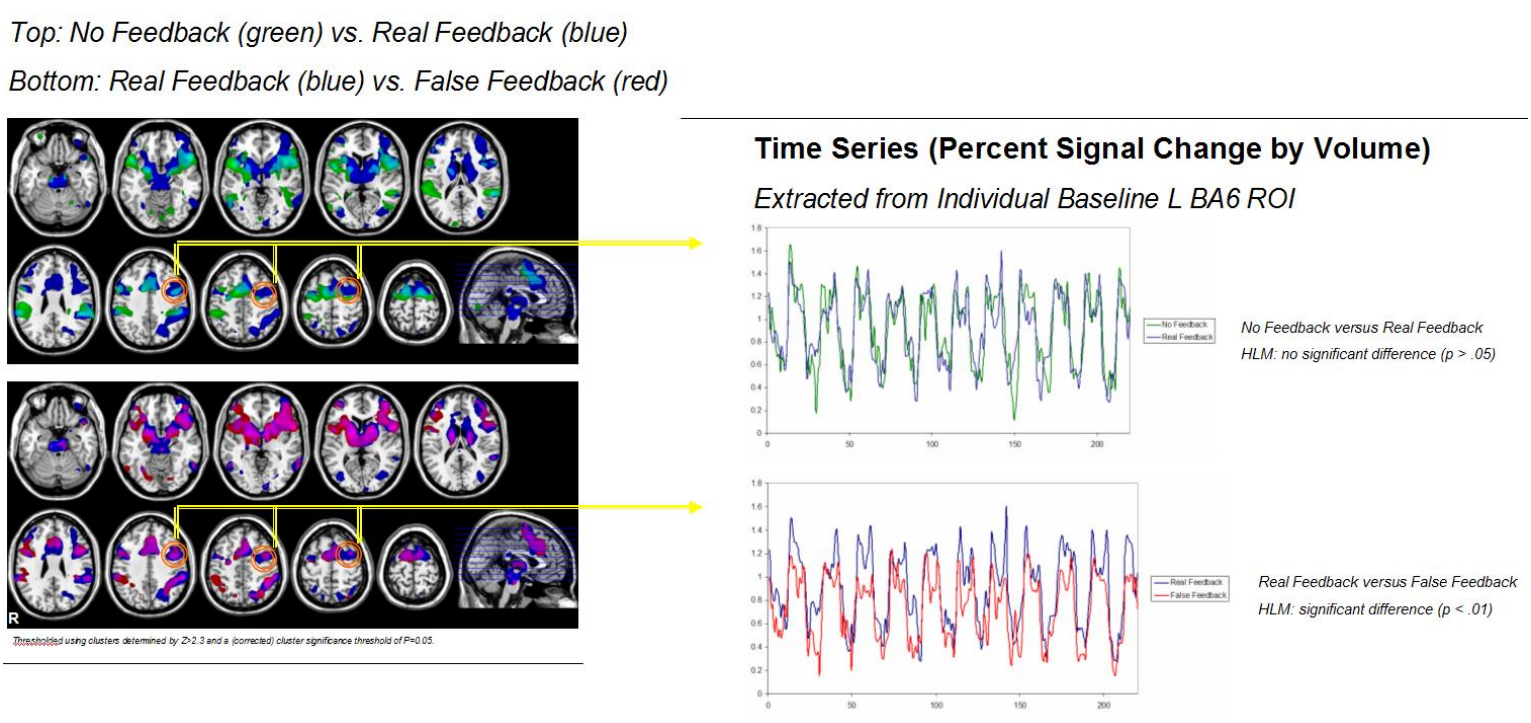

Figure 4: Brain activity was measured during an Imagine Movement Task for the first baseline scan (No Feedback) and for the second and third scans (Real or False Feedback, in counterbalanced order). The percent signal change (PSC) was extracted from L BA 6 (left of figure) and compared for the various conditions (right of figure). No significant difference was found between the baseline No Feedback PSC and the Real Feedback PSC (top right of figure). False Feedback PSC was significantly less than Real Feedback PSC (bottom right of figure).

The decrease in the spatial amount of activity from the baseline imagine-movement task may be related to fatigue or practice effects. However using real feedback, participants maintained a brain-activity correlated signal that did not differ from baseline for the specific brain region of interest. This early work suggests that brain feedback may be used to maintain performance despite fatigue.

We are currently exploring additional parameters that may enhance training with brain feedback. We are testing whether continuous or intermittent feedback is more effective. Continuous feedback provides the participant with more frequently updated feedback, but may distract the participant from the task or confuse the participant with a delay between actual and measured brain activity. Intermittent feedback provides less frequent information to the participant, but may not have the drawbacks of continuous feedback.

7.0 SUMMARY AND CONCLUSIONS

An extensive amount of work has been focused on accurately predicting which flight-school candidates will succeed and which ones will fail. Prior to 1953, the Air Force and its predecessors ran no true flight screening program, and at one time or another, only 32% of trainees actually earned their wings. Needless to say, the time and effort wasted on candidates who ultimately failed to become serviceable pilots spurred significant interest in developing accurate qualifying measures. However, after 40 years of effort, the predictive validity of aircrew screening systems remains far from perfect. The pilot composite of the US Naval Aviation Officer Selection Battery has a validity correlation of 0.15-0.25, and the Air Force Officer Qualifying Test (AFOQT) has predictive validities in the same range. Such low correlations are in part responsible for the fact that flight-trainee attrition rates hover around 15 percent despite efforts to hold these rates within the 8-10 percent range. Given that the current cost of training a single jet pilot is approximately $1.5 million dollars, it is easy to see why additional improvements in our ability to rapidly and accurately identify optimal pilot candidates are necessary.

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